

# INVESTIGATIONS ABOUT THE QUANTITATIVE CHANGES OF CARBON DIOXIDE PRODUCTION IN HUMANS

## Report 2.

## Carbon Dioxide Production During Fever and Its Relationship with

## ~~Heat Production~~

by

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INVESTIGATIONS ABOUT THE QUANTITATIVE CHANGES OF CARBON DIOXIDE  
PRODUCTION IN HUMANS

/153

by

Dr. C. Liebermeister\*\*

Report 2

Carbon Dioxide Production During Fever and Its Relationship  
With Heat Production.\*

At the present time, for heat production during fever, we generally believe that there is an increase in heat production during the chill stage as well as during the heat stage. Traube formulated a new theory of fever and later on formulated the peculiar hypothesis that during fever there is not only an increase in heat production, but also a restriction in the amount of heat expelled. Recently, certain authors quote the theory of Traube and defend the assumption according to which there is an increase in heat production [1].

For the chill stage of fever, it can be demonstrated with certainty that there is a reduction in the heat loss, and there is also a very substantial increase in heat production [2]. For the heat stage, the Traube theory does not seem plausible to begin with. The assumptions for it can be directly contradicted because in lukewarm and cold baths, fever patients give off much more heat than healthy persons.\*\*\* It has been possible to directly prove the increased

/154

\*Contains Tables II and III.

\*\*Professor in Basel.

\*\*\*From the Medical Clinic in Basel. Observations and experiments about the application of cold water for fever patients. Leipzig, 1868, p. 124. It has been suggested that I should not have compared heat expulsion of fever patients and healthy persons for absolutely the same bath temperatures, but instead for the same differences between the body temperature and the bath temperature. I believe that this requirement is based on a misinterpretation of the question involved. In order to disprove the Traube assumption, it is not at all necessary to prove that fever patients give off more heat for the same temperature differences compared with healthy persons. This question is of interest for other reasons. It is only necessary to demonstrate that for completely equal external conditions, the hotter skin of the fever patient gives off more heat than the cooler skin of the healthy person. As is well known, one usually heats rooms with fever patients more than rooms for healthy persons. In the following I will discuss this in more detail.

heat production of fever patients for one case, the case of a lukewarm bath, where the heat production of the healthy person corresponds to the norm.\* Finally, Leyden used calorimetric determinations of amounts of heat given off by parts of the body surface and demonstrated that there is an increase in heat output for fever patients [3].

The increased heat production of fever patients of necessity would have to be attributed in the final analysis to an increase in the metabolism. This assumption is also corroborated by results of numerous urea investigations. If they were carefully performed, they all showed that this end product of metabolism of substances containing nitrogen are excreted in much higher volumes in the case of fever patients.

Recently, the proof of this fact has been questioned. For diabetes mellitus, /155 which was already mentioned by Traube [4] in this connection where large amounts of sugar are excreted which have not been burned, it is natural that the increase in the urine production does not allow the conclusion that there is an increase in the total metabolism. However, the possibility has not been excluded up to the present that there is only partial oxidation of components containing nitrogen in the case of fever patients. It is possible that due to the substantial body temperature increase there will be a substantial sweating of albuminates with the formation of fat, and the latter would then not be completely oxidized.\*\*

The question of the behavior of other end products of the metabolism is much more important, in particular the behavior of carbon dioxide during fever. The quantity of carbon dioxide is greater than all of the other oxidation products put together. In healthy persons, there is 20 times as much as there is urea. Therefore, one can doubt whether carbon dioxide is a better measure for the total.

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\*L.c., P. 128. In this case a comparison for equal temperature differences would have a certain justification, because large temperature differences would result in increased heat production even for fever patients. However, since it has been demonstrated that this regulation is not so productive for fever patients, the conditions would become very complicated and cannot be completely described without other conditions.

\*\*I would like to recall some facts. First of all, with a continuous temperature increase there is a parenchymatous (sometimes fatty) degeneration of numerous organs (see this publication, Vol. I, p. 328). On the other hand, the investigation of Bartels and Vaunyn showed that even artificially induced temperature increase without fever results in an increase in urea production. The probability that fat is formed from albuminates has been greatly increased because of the work of Voit.

metabolism and heat production than is the urea excretion.

Previous investigations about the variation of carbon dioxide production during fever indicate that there is an increase. This is true for almost all of the older investigations. Even the newer investigations of Senator with animals with artificially produced fever showed that the carbon dioxide was never increased, but instead was decreased. The author grants the point that much was left to be desired in the accuracy of the experiments. From the other tests, where no determinations of carbon dioxide were made at all, the corresponding result is only obtained by a erroneous or arbitrary calculation [5].

/156

On the other hand, already in the introduction of the first article (Vol. VII, P. 76), I mentioned that during the attacks of two alternating fever patients there was a substantial increase of the amount of carbon dioxide produced. Leyden also recently found increased carbon dioxide production during fever, using a somewhat modified Lossen method.\*

#### Carbon Dioxide Production for Alternating Fever Attacks

The following investigations were made using the apparatus discussed in the first article.

It is important to recall the fact that individual carbon dioxide determinations in fever patients or also a series of them usually does not give a result, because there are no absolute numbers which could serve as references for comparisons. It would not be correct to expect the same or even greater amounts of carbon dioxide in the case of a fever patient who only eats a small amount of food and lies in bed, compared to a normal person with a normal amount of food. It is easily seen, as I mentioned earlier, if one wishes to compare metabolism and heat production of a fever patient and that of a healthy person, then one must not use a healthy and active person for this comparison. Instead, one should use a healthy person with the same body weight, who also lies in bed just like the

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\*Centralblatt f. d. med. W. 1870. No. 13. This work of Leyden has appeared since that time (this archive, Vol. VII, P. 536, ff) and in my view there is no doubt that the carbon dioxide production was increased during fever. These observations are for the case of Febris recurrens (exanthematic typhoid and pneumonia).

fever patient and is covered in the same way [6].

For this reason, for comparative investigations, patients are especially well- /157 suited where the fever attacks and apyrexia alternate several times.

First, I will discuss observations of patients having intermittent fever. This illness is very rare in our country and usually only occurs in patients coming from other places and have recurrences here. The very severe cases usually do not occur in our country. However, these observations should suffice to emphasize the main points.

1. In the case of a 22-year-old carpenter from Holstein (Laage) who was afflicted with Febris tertiana, carbon dioxide excretion was investigated twice during the fever attack and during the apraxia. Each of these four tests were set up so that the patient was in a box for two hours lying down. During this time, the quantity of excreted carbon dioxide was determined for this time period. The body weight of the patient was 62.7 kg during the first test series and 61.6 kg during the last test series. All of the tests occurred during the morning and equal conditions were provided during the individual test series as much as possible.

In the first test, on June 6, 1869 (fever attack), the armpit temperature 43 minutes before the beginning of observation was  $38.1^{\circ}$  (C). At the beginning of the test it was  $39.5^{\circ}$ , then rose to  $40.5^{\circ}$  in the next 40 minutes and stayed there. Nine minutes after the end of the test, it dropped to  $39.9^{\circ}$ . At the beginning of the observation, the chill had already stopped. Therefore, the test includes the heating stage. The beginning of the test is the increase time interval and the end of the test corresponds to the temperature drop phase.

During the second test on June 9 (apraxia with well-being) the temperature in the armpit was  $37.0^{\circ}$  before and  $36.4^{\circ}$  after the test.

In the third test, on June 10 (fever attack), the attack had started three hours before. The armpit temperature was as much as  $40^{\circ}$ . Before the beginning of the observation, it dropped somewhat and 38 minutes after the end of the test it dropped to  $38.3^{\circ}$ . Already at the beginning of the test there was a slight indication of perspiration and after this a massive perspiration excretion. The

test, therefore, includes the beginning of the perspiration stage.

The fourth test, on June 13, again covers the apraxia time period. On June 11, the patient had taken 1-1/2 grams of Chinine. There was no fever attack on the 12th.

The results are given in the following table.

The carbon dioxide production was as follows:

/158

	June 6 Fever attack heat stage	June 9 Apraxia	June 10 Fever attack perspiration stage	June 13 Apraxia
in the 1st half hr.	20.7	13.8	19.6	16.1 g
in the 2nd half hr.	19.2	15.0	17.8	16.9 "
in the 3rd half hr.	19.0	14.6	18.8	15.1 "
in the 4th half hr.	<u>18.7</u>	<u>14.7</u>	<u>17.3</u>	<u>15.8</u> "
in two hours	77.0	58.1	73.5	63.9

During the duration of the fever the carbon dioxide production was greater than in the stage without the fever. Of all the values observed for the individual half hours during apraxia, there is none which reached a low level of values obtained during the fever stage. Whether we use the second or the fourth test series for comparison, we find that in the first series which, for the most part, corresponds to the heating stage, there is an increase in the carbon dioxide production by 21 or 34%. For the third series, which corresponds to the beginning of the perspiration stage, there is an increase by 15 or 27%.

2. For a short time period, a 20-year-old girl was suffering from tertian ague. Four carbon dioxide determinations were made at the same time of day. All tests were made between 4:00 and 7:00 o'clock in the afternoon. During the first time the patient weighed 57.2 and during the last test she weighed 56.1 kg.

The first test, on August 2, 1869, was during the apraxia period. After it the temperature in the armpit was 36.5°.

The second test was performed during the fever attack on August 3rd. The

armpit temperature 35 minutes before the beginning of the observation was 38.7°. Very soon after this there was a massive freezing. The temperature increased slowly and 85 minutes after the beginning of the observation it reached 40.9°. It then stayed at this level and 35 minutes after the end of the two-hour test, it had dropped to 40.4°. Therefore, the test coincided with the chill and heating stage.

The third test, on August 5, again was taken during the fever attack but during a later period. The armpit temperature 20 minutes before the beginning of the observation was 41.1°. At the beginning, we could already detect a slight drop and 25 minutes after the end of the two-hour test, the temperature was 39.9°. It was dry heat up to the third half hour and slight perspiration at the end of the test. Therefore, the test coincides with the perspiration stage.

The fourth test, on August 6, again was during the apraxia stage. The armpit temperature was 36.9° during it.

The attacks disappeared altogether after 1-1/2 grams of quinine was administered.

/159

The carbon dioxide production was the following:

	August 2 Apraxia	August 3 Fever attack chill & heat stage	August 5 Fever attack perspiration stage	August 6 Apraxia
in the 1st half hr.	13.0	17.0	13.9	13.6 g
in the 2nd half hr.	13.3	18.8	13.8	15.3 "
in the 3rd half hr.	14.0	17.3	15.0	14.8 "
in the 4th half hr.	--	16.2	14.2	-- "
in two hours	53.7	69.3	56.9	58.3

The comparison of the two test series shows the result obtained for the other patients for fever attacks, and approximately 29% greater carbon dioxide production than found apraxia. On the other hand, during the third test coinciding with the beginning of the perspiration stage, the carbon dioxide production was not greater than during apraxia.

These experiments already demonstrate that in general the carbon dioxide production is greater than during apraxia during a tertian ague attack.

A detailed analysis, however, shows some relationships which are remarkable and do not agree with the usual assumptions made.

First, it is apparent that even though more carbon dioxide is excreted at a higher body temperature than at a low body temperature, there are substantial exceptions to this rule. The assumption of a constant ratio of the body temperature and the carbon dioxide production cannot be made. In the test of August 5, for example, the body temperature was between  $41.1^{\circ}$  and  $39.9^{\circ}$  during the entire test; nevertheless, the carbon dioxide production was not greater than during tests where the temperature was less than  $37^{\circ}$ .

Also, it might appear that the demonstrated increase in the carbon dioxide production during fever is smaller than one would have expected if one assumes that the magnitude of carbon dioxide production is approximately an indicator of the amount of heat produced. In any case, most authors have the tendency to assume that the heat production increase during fever is more than one-fourth or a third of the normal production. When calculating the heat production in the chill stage of tertian ague, it was found that it had increased to three times the normal production [7].

I already stated that one has to assume a completely different variation of the heat production and the heat loss if a human being is rapidly brought from a normal temperature to a higher temperature, compared with the case where a body at an abnormally high temperature is maintained at the high temperature [7].

One can only gain an understanding of this complex question if we discuss in detail the theoretical conditions of heat production in fever patients. These conditions are very complicated and difficult. However, they are accessible to a physical treatment. In this discussion, we must distinguish among the various stages of fever.

#### Heat Balance During the Heating Stage

First of all, let us consider a phase where the temperature remains about

the same continuously, the so-called heating stage, which in the case of tertian ague only lasts a few hours. In other fever patients, it can last several days or months.

If a fever patient with an internal body temperature of about  $40^{\circ}$  maintains this temperature for some time, then the heat production and heat loss will be in equilibrium. He produces as much as he expends and, therefore, the heat reserve in the body remains about the same continuously. In this regard, the fever patient is under the same condition as a healthy person. The only difference is that this equilibrium state occurs at a higher absolute temperature in the case of the fever patient.

How does the heat loss of a fever patient during the heating stage vary compared with the heat loss of a healthy person? /16.

If one feels the hot skin of a fever patient, then it is easy to forget that this is an increase of only a few degrees. One is inclined to estimate that the amount of heat with such a skin must lose to its surroundings by conduction and radiation as very high, compared to the loss of a healthy person. However, a simple calculation shows that this excess is always substantial but less than one commonly assumes.

For comparison, we will make several simple assumptions: we assume that everything else is the same and allow a single difference that the internal body temperature of a healthy person is  $37^{\circ}$  and it is  $40^{\circ}$  for the fever patient.

The heat loss due to conduction and radiation is proportional to the temperature difference. For the present case, it is proportional to the difference between the temperature inside the body and the temperature of the outside air.\*

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\*One could believe that it is not correct if we use the difference between the temperature of the internal and external air for comparing the heat loss. One could assume that instead one could use the body surface temperature and the temperature of the air between the skin and the clothes. The last calculation should give a correct result if the quantities are determined correctly. As a closer analysis using ordinary physical laws shows, the result is of necessity the same as in the calculation given above. For example, let us assume that the temperature of the air between the body surface and the clothes or cover is  $25^{\circ}$  for healthy persons. Of necessity, it will have to be higher for fever patients, say  $26^{\circ}$ . In addition, let us assume that the temperature of the skin of healthy persons is 2 degrees lower on the average than the temperature inside. If every-

Let us assume that the outer air temperature is  $20^{\circ}$ . Then the heat loss of the healthy person compared with the patient is in a ratio of 17 to 20, if it is based on conduction and radiation. The fever patient, therefore, would lose about 18% more heat by conduction and radiation. /162

The total heat loss is composed of loss over all the members. The water evaporation has a distinct influence on this. This is subject to major fluctuations, both for fever patients and normal persons. If it increases by the same ratio and if the other less important factors of heat loss also increase, then the heat loss of a fever patient with a continuous temperature of  $40^{\circ}$  would of necessity be about 18% higher than the heat loss from a healthy person. In order to maintain the temperature constant, the fever patient would have to heat his body more, in such a manner that he would consume about 18% more fuel.

However, we will admit the fact that usually the assumptions of the calculations are not completely satisfied, and in reality conditions are also not exactly the same. In addition to the numerous conditions of varying importance, which bring about either an increase or a reduction in the heat loss, during the heating phase there are several times when these factors act together to increase the heat loss. The more pronounced ventilation of the lungs is one of these factors. In addition, during the heating phase the average temperature of the skin is somewhat less than the temperature of the inside of the body because of the increase in size of the skin vessels. Therefore, the heat output will be somewhat larger than would logically follow. Often, the water evaporation increases more than would be a consequence of heat loss by conduction and radiation. Therefore, the calculated value should be looked upon as a minimum value for the heat phase. Under usual conditions, the heat loss is slightly higher.

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thing were the same, it would have to be more than 2 degrees lower for a fever patient. Therefore, we obtain a ratio of 10 to somewhat less than 12. The heat loss of the fever patient would have then been increased by less than 20%. The assumption of the differences in the behavior of both individuals also changes the result. If we assume, which often corresponds to reality, that the average skin temperature is somewhat different from the temperature inside due to the expansion of the vessels of the skin in the fever patients, let us say only  $1-1/2$  degrees lower, then the increase would amount to 25%. If, in addition, due to the light covers over the fever patient, if the temperature between the air and the covers was not greater than  $25^{\circ}$ , then a heat loss increase of 35% would result (it also follows that the skin temperature would decrease somewhat, which we will not consider here).

If one calculates the increase in the heat loss for each degree of temperature, for which there is also an equivalent equal increase in the heat production for the same body temperature, then we obtain the following heat production of the fever patient during the heating phase for the following temperature: /163

38°	an increase of about 6 percent or more
39°	" " " " 12 "
40°	" " " " 18 "
41°	" " " " 24 "

Of course, these numbers are only averages which can only be applied in special cases if one is certain that none of the conditions exist which would have a major influence on the heat loss.

The assumption made in the above calculation that the heat output of a human is proportional to the difference between his temperature and the surrounding medium if this heat loss occurs due to conduction and radiation, is based on general physical principles. For the special case where the surrounding medium is water, this assumption and the entire calculation can be checked by an experiment. Such an experiment is to be recommended because even the most exceptional scientists are often not inclined to test simple physical laws governing the conditions for fever. They sometimes believe that fever patients are subjected to special conditions in addition to the measurable changes in the conditions, and they say that a heat economy will no longer correspond to the usual physical laws. In the case of living organisms, we must always be prepared for complicated conditions. But simple resignation would not produce much progress, nor would simple reasoning which would ignore the existing conditions.

Earlier, I discussed investigations about the heat loss of fever patients in lukewarm and cold baths,\* and the results can be compared with the assumptions for the above calculation.

In order to compare the heat loss of fever patients with that of healthy during baths, the conditions are very favorable because the highly influential humidity and evaporation conditions of the skin drop away completely. Nevertheless /164

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\*From the Medical Clinic in Basel, pp. 103, ff.

less, the conditions are not very simple, and if one takes arbitrary numbers without further thought, then one should not be surprised if the results obtained are absurd. .

The heat loss during the first minutes of a bath for the most part corresponds to the "peripheral cooling" and depends substantially on the skin temperature caused by random influences before the bath. Therefore, I do not consider the first five minutes and will only use the following 15 minutes for comparisons. (See cited work, p. 121, Table A, Col. V.)

In the same way as was done above for usual conditions, in any individual observation one can calculate how large the heat loss of the fever patient should be according to the heat loss increase theory, compared to the heat loss in healthy persons in a bath with the same absolute temperature. The result obtained by calculation can then be compared with observations. We assume that everything else is the same and assume that the difference between the fever patient and the healthy person is only due to the fact that the observed temperature in an individual fever patient case is  $(40.1^\circ - 40.9^\circ)$  and that the average observed temperature of healthy persons is  $37.2^\circ$ . We will not consider the substantially enlarged skin vessels of the fever patient for the time being.

I will carry out the calculation with several examples. Let us calculate the theoretical heat loss of a fever patient at  $40.5^\circ$  in a  $34.3^\circ$  bath. The difference between the body and water temperature is  $6.2^\circ$ . A healthy person with  $37.2^\circ$  in the same  $34.3^\circ$  bath would only experience a temperature difference of  $2.9^\circ$ . Accordingly, the ratio of the fever patient loss to the healthy person loss would be 6.9 to 2.9. Therefore, it must be 2.14 larger or be increased by 114%. Observations on healthy persons in  $34.3^\circ$  baths show a heat loss of 17 calories. From this we can calculate a heat loss of 36 calories for a fever patient. Our observations showed a value of 37 calories. Or let us consider a fever patient at  $40.1^\circ$  in a  $28.1^\circ$  bath. What is the theoretical heat loss? The temperature difference is  $12^\circ$ . For a healthy person at  $37.2^\circ$ , the difference is  $9.1^\circ$ . The heat loss of the healthy person divided by that of the fever patient must be in the ratio of 9.1 to 12. It would have to increase by 32%. The healthy person in a  $28.1^\circ$  bath experiences a loss of 53 calories. The calculated loss of the fever patient is 70 calories. Our experiment gave 68 calories. This agreement between the calculation and the observation was not as complete in all experiments. Under these conditions, we would not have expected this a priori.

In the following tables, the third column is the heat loss which the healthy person experiences in the bath at a given temperature between the 6th and 20th minute. One obtains this heat loss by multiplying the temperature difference with 5.84. This factor is the average value from all observations of healthy persons. The fifth column shows how much higher the theoretical heat loss of a fever patient should be above that of a healthy person in percent. The next to last column gives the theoretical heat loss of the fever patient (the numbers in this column could also be calculated directly from the temperature difference and the factor obtained for healthy persons. However, we were interested to clearly demonstrate the enormous differences in the percentages, in addition to the agreement between the calculated and the experimental values). The last column gives the values found in experiments for comparison with the calculated values. All numbers are reduced to the same body surface, so that they correspond to a 50 kg body weight (see cited work, p. 120 ff). The heat removal through the lungs and through the head not in the water is not considered. /165

Subject	Temp. of the bath	Heat loss of healthy persons	Temp. of patient	Theoretical increase for fever patients in percent	Heat loss of fever patients Calculated	Measured
H1	34.5	16	40.7	130	37	39
H1.	34.3	17	40.5	114	36	37
B.	32.3	29	40.2	61	47	32
D.	31.8	32	40.2	56	50	50
H1.	29.6	44	40.4	42	62	87
Hr.	28.1	53	40.1	32	70	68
B.	24.1	77	40.9	28	99	90
H1.	23.0	83	40.4	23	102	132
D.	21.5	92	40.1	18	109	139
Hr.	20.0	100	40.7	20	120	140

It is important in the evaluation of the degree of correspondence between theory and calculation to consider the fact that the observations were made with four patients (three with abdominal typhoid and one with pneumonia). One of these patients had a body weight of 38 kg and another 75 kg. In single experiments, observational errors of up to 4 calories occurred, and sometimes even larger errors could not be avoided. When the values were reduced to the same body surfaces, they were sometimes increased. The agreement between the calculation and

the observation is quite satisfactory if one considers the large range of the experiments. According to the heat output theory, the fever patient's heat output should be greater than that of a healthy person by more than 100%, i.e., it should be twice as large. In colder baths it is expected that it will be only between 18 and 20% larger. For the seven first observations, where the sum of the calculated heat output was 401, the sum of the measured heat output was 403. We should like to remark that the large differences which do occur (B. 32.3 and H1. 29.6) can be partly explained due to the special condition, as I already mentioned in the discussion of the observation (cited work, p. 124). /166

The agreement is not so good for the last three observations where the result of the calculation and the observation are in a ratio of between 10 and 12. The fact that the deviation was in the same direction in the cold baths for all three individuals seems to indicate that some factor is effective which was not considered up to the present. I can assume that this has to do with the circulation in the skin. The observed deviation could be completely explained if we assume that the fever patient experiences a contraction of the skin and its vessels in the cold bath, so that the heat loss is restricted, but that this effect is not as great as in a healthy person.

This assumption can be supported by another factor. Let us compare the numbers for the healthy person and the fever patient at different bath temperatures, and let us consider the heat loss per degree of temperature difference. For the healthy person for baths between  $35.8^{\circ}$  and  $22.5^{\circ}$ , dividing the heat loss by the temperature difference, we obtain the following quotients starting at the warmer baths and going to the colder baths:

From the 6th to 15th Minute:	5.0	4.4	4.2	4.4	4.2	3.4	3.5
From the 6th to 20th Minute:	8.6	6.8	6.3	6.2	5.8	4.9	--

In general, the uniformity of these numbers expresses the approximate proportionality between the heat loss and the temperature difference. But the slow decrease of both series towards the low temperature baths also demonstrates how the heat loss slowly becomes smaller compared with the temperature difference, the colder the baths involved. And this behavior, which no longer corresponds to general physical laws, can only be explained by the assumption of different con-

ditions. The simplest explanation is the assumption that the circulation in the skin is restricted more and more as the bath becomes colder.

This severe restriction of the heat loss in the colder bath is not the same for the fever patient. For baths between  $34.5^{\circ}$  to  $20.0^{\circ}$ , we obtain the following quotients starting at the warmer baths and going to the colder baths:

From the 6th to 15th Minute: 4.5 4.8 2.8 4.0 5.9 4.1 4.0  
5.3 5.4 5.0

From the 6th to 20th Minute: 6.3 6.0 4.1 6.0 8.1 5.7 5.4  
7.6 7.5 6.8

Except for the large irregularities, these series agree quite well with the first part of the values obtained for healthy persons. They also show an approximate proportionality between the heat output and the temperature difference. However, /167 there is no decrease towards the colder baths as was the case for the healthy persons. Instead, there is a slight increase.

If one carries out the same calculation in comparison between the theoretical and actual heat loss of a fever patient as was done above for the 15 minutes, for the 10 minutes between the 6th and the 15th minute, we obtain a completely similar result. The agreement is just as satisfactory. However, already at the beginning, the calculated quantities are slightly smaller than the measured values. Just like in the previous calculation, the difference becomes large enough to come outside of the error band only for the cold baths (the last three observations).

The calculation of the five minutes between the 6th minute and the 10th minute gives a completely similar result.

However, there is a substantially different result which involves the comparison of the first five minutes of the bath. If one compares the heat loss for the same temperature difference for this time interval; then one finds that for the fever patient, it is substantially greater than for a healthy person, on the average by about 37%. Part of this difference can probably be explained by our earlier assumption according to which the body temperature of the fever patient before the bath differs less from the surface temperature than it does in the healthy person. The relatively warmer body surface must then give off

more to the bath during the first interval of time. However, in order to use this factor to explain the entire difference, then the temperature difference between the surface and the inside of the fever patient would have to be more than  $2^{\circ}$ . Therefore, another factor must be used to explain this. This factor is found if we use the assumption that the skin contraction and the vessel contraction is not complete for the fever patient. It is a protection against excessive and intensive cooling in the healthy person. In tests on fever patients in cold baths the "peripheral cooling" was always found to be exceptionally large. These factors contribute to a reduced regulation of heat production. A fever patient is more capable of reducing his inside temperature by removing heat than is a healthy person.

By considering the circulation, we can explain all deviations from the proportionality law between heat loss and temperature difference which occur in baths in healthy persons and in fever patients. At the beginning of the bath, the cooling is more intense for a fever patient due to the defective contraction of the skin vessels. Later on during the bath, the surface is cooled more and to a lower temperature and this fact protects the body against further cooling. During this later time period, any defect in the skin vessel contraction is made noticeable by the greater heat loss in cold baths.

From the tests and calculations discussed, we find by carefully considering /168 the conditions of heat loss of a fever patient and of a healthy person, we can reduce the process to simple physical laws. In water the heat loss of a fever patient is proportional to the temperature difference just as in a healthy person. However, in order to consider the loss complete, the temperature existing at any time and at any location of the body would have to be taken into account. If one calculates with the internal temperature, then the result is only completely accurate if everything else is completely the same. Due to the differences in behavior of the skin and its vessels, deviations from the simple law come about. These are relatively small and not capable of covering up the law. In order to completely understand this law, one has to consider these changed conditions. The fever patient loses more heat compared with a healthy person under otherwise equal conditions because his body temperature is higher. Therefore, the temperature difference between the body surface and the surrounding medium is greater. Due to the expanded skin vessels and a facilitated heat conduction to the skin from the inside, the heat loss is increased even more because this increases the

temperature difference.

Of course, one should not directly transfer values found from water to air, because the absolute heat loss depends substantially on the heat conductivity and the heat capacity per unit volume of the surrounding medium. However, one can transfer the general proportionality law between temperature difference and heat loss, if it has been established for one medium. Therefore, these experiments on the heat loss in baths provide the experimental proof for the correctness of the assumptions which were the basis for calculating the heat loss for the heating phase of fever under ordinary conditions.

The experiments used in these calculations on heat losses in the baths were used soon after their publication elsewhere for comparing the heat loss of fever patients and their heat production. However, this was not successful. Senator\* /169 calculated from my experiments that the ratio of heat loss of a healthy person to the one with intense fever is 100 : 172. From this, he concluded that the heat given off by a severe fever patient with an average temperature of  $40 - 41^{\circ}$  would have to be at least 1-1/2 times greater than under ordinary conditions. According to his calculation and for intensive fever, the ratio of the increase in the heat production would have to be at least 100 : 135. Therefore, he reaches the following strange conclusion: the heat production is much less than the heat output even under the heat of fever!

The author himself seems to have suspected the rebuttal to this contradiction because he continues as follows: If in addition to the above additional factors were to come into play, then one necessary consequence would be that the temperature would have to drop continuously. Accordingly, everyone would conclude that the calculation given above is false. Either the compared numbers do not match or one of them is wrong, or both are wrong. However, this would have been too simple. Senator reaches the following conclusion. Accordingly, according to our present state of knowledge, and as long as other factors have not been discovered or made plausible, only one assumption can be made, offered by the Traube theory: Holding back of heat is very important for a fever patient. One must assume that during the heating phase there is a restriction in the heat loss once

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\*Virchow's Archive, Vol. 45, P. 399 ff. I discussed elsewhere the other two sections of this article which are concerned with the physiological heat regulation.

in awhile in addition to the continuous heat production which is increased due to albumin metabolism. It is only by an interaction of both causes that an equilibrium in the heat balance is established over long time intervals, so that a certain average level can be maintained. The restriction of the heat loss is due to the contraction of the contractive skin elements, i.e., that is the small and tiniest arteries. This is expressed by fever chill. This can occur by a change in the nature of the skin without any sensation or shiver. Perhaps these words say that in reality there is no absolute continuous fever and instead there are more or less expressed remissions and outbursts in any continuous fever. Perhaps they say that fever patients easily show increasing temperature factors ("chill phase" without actually showing chill). If this is so, then the author has used confused words to express a generally well-known fact which has never been doubted. It then becomes difficult to understand how this everyday fact must be reconciled with the above calculations. However, if other ideas are behind these confused words, then I do not wish to clarify them here. /170

Let us now consider the calculation of the heat production and heat loss during fever performed by Senator.

The calculation of the heat production was made with the assumption that during fever there is no increase in the carbon dioxide secretion, but only an increase in the urea. If one really calculates with this assumption and if one uses the number for the combustion heat of Frankland for albumin, then one finds that there is no increase in the heat production at all. How it was possible for Senator to nevertheless obtain an increase in heat production by as much as 35% should be looked up in the original text. I would only like to state that again this is a calculation error, which as is well-known occurs very often with this author. He forgot to consider the carbon dioxide which is formed during the oxidation of albumin.

I can be brief about the calculations of Senator made according to my results about the increase in the heat loss, because consideration of my discussion above will suffice to show that this is a continuous series of errors. Comparisons were made between the heat losses of the fever patients and healthy persons during the first five minutes of the bath. Then the numbers found for the stay in the water were looked upon as valid for ordinary conditions without any further reflection. However, comparison was not made for the same bath temperature, which would have made sense here, but for the same temperature differences. This is not

even done in an orderly fashion. Instead, Senator assumes that in my table the lower water warmth is valid for the healthy persons in all cases and the next higher number is valid for the fever patients. Finally, his result depends on the random factor, how closely the different bath temperatures occur in my table. However, if he had only followed his wrong assumption and had really used the numbers, he would not have found what he was looking for, but 72% instead of only 37%. This is a number which by a strange coincidence is exactly as large as the erroneously calculated number for the increase in the heat production. He would have then been spared from a fatal physical dilemma. But then the material for his section on the theory of fever would have been missing.

After this discussion about the heat production during the heating phase, using the results obtained we can make comparisons using results from previously reported investigations on carbon dioxide secretion.

In the first patient, only the first test period coincided with the phase of equal temperature, and this only included the third and perhaps the second and fourth half-hour. The temperature was between  $40^{\circ}$  and  $40.5^{\circ}$  but the carbon dioxide production had been increased by between 19 and 31%. According to our calculations, the temperature given should have corresponded to an increase in heat production by between 18 and 21% or more. /171

In the second patient, the last half-hour of the second test series, coincided with the heating phase. The carbon dioxide production was increased by 21%. At the temperature of  $40.9^{\circ}$ , the heat production should have increased by 23% or more.

Therefore, the observed increase in the carbon dioxide production agrees very well with the calculated increase in heat production. In the first case, the increase in the carbon dioxide production was slightly larger and in the second case it was slightly smaller.

In earlier discussions we pointed out that the calculated values for the heat loss and heat production in the heating phase should only be looked upon as averages. They are only valid when the calculation assumptions are approximately satisfied. Very large deviations can occur in individual cases. This is because in the case of the fever patient there are many more circumstances compared with a healthy person, which could lead to a much lower heat loss or a much higher

heat loss than the calculated average. I would only like to mention the state of the heart or the magnitude of the work performed by the heart as well as the degree of contraction of the skin vessels. These are two factors which determine the circulation in the skin and therefore the rate of heat equalization between the inside and the periphery. Also there is the yield of the lung ventilation, the perspiration magnitude, and the sensed perspiration, as well as many other external factors.

Under certain conditions, some of these factors can already influence the heat loss during the heating phase. In the case of very long duration, continuous fever where the heart activity usually drops and sometimes to a very low level (see this publication, Vol. I, p. 462 ff) and where the skin is often very dry, /172 it may happen that the heat loss will drop far below the assumed average value and even under the norm, for example during the later period of abdominal typhoid. On the other hand when there is energetic Hertz, a large turgor and a high degree of skin humidity, or when there is even perspiration, it is possible for the heat loss and heat production to increase drastically even when the temperature remains the same.

The largest deviations occur during those phases of fever where the temperature does not remain approximately constant, but is either rising or dropping.

We will first consider the sinking temperature phase where the temperature drop is rapid. Usually, this is accompanied with a large amount of sense heat perspiration and this is called the perspiration phase.

#### Heat Balance During the Perspiration Phase

The temperature drop during this phase shows that the heat loss is greater than the production. The heat loss is usually substantially greater than according to our earlier calculation for the corresponding temperature. First of all, the relaxation of the skin and its vessels contribute to this loss, as well as the facilitated heat equalization between the inside and the surface. In addition, the water evaporation increases drastically because of the wetness of the skin and the possible perspiration. In addition, the body surface is not covered as densely. It would be possible to approximately determine how large this in-

crease in the heat loss is for given conditions and assumptions. In order to make a comparison with our carbon dioxide determinations, which are dubious especially for the case of perspiration, we note that during this phase the heat loss can have increased quite drastically, up to several times the normal loss.

It is not possible to determine a priori how the heat production varies. When the heat loss increases drastically, it is possible for the body temperature to drop and there can be reduced or normal and even increased production. In the latter case, the increase in the heat loss must of necessity be greater than the increase in production.

/173

Among the experiments on carbon dioxide secretion, we have two which occur during the decrease in temperature phase. However, both cover the beginning of the perspiration phase and the drop was not very rapid in both cases. In the first patient (third test series) the carbon dioxide production was even increased by between 15 and 27%. In the second patient (third test series), in spite of the large body temperature which was dropping starting at 41° to 40°, the carbon dioxide production was not larger during the phase with no fever. It follows from this that at the beginning of the perspiration stage, there is increased carbon dioxide production and normal carbon dioxide production.

Let us take the carbon dioxide production as a measure for the heat production and we will use a factor which will be discussed in the following. For the first patient for the two hours of observation we obtained a heat production of 235 calories. From the observed drop in the body temperature, we find that the heat loss was larger by about 67 calories. It amounted to approximately 302 calories. Therefore, at the beginning of the perspiration stage, the heat production was about 21% larger and the heat loss was about 55% larger above apraxia (average from both observation series). The substantial increase in the heat loss is not surprising, because the patient had an increased temperature and also a slight indication of perspiration. Later on, there was a massive perspiration. This is also due to the fact that the way he was covered was entirely up to him.

In the other patient during the second hour the heat production was 182 calories and the heat loss about 229 calories. The heat production was approximately equal to the average obtained during apraxia. The heat loss was greater by about 26%. At the existing temperature, this is a number which only represents

a slightly high average for the heat loss during the heating stage. In this patient there was dry heat up to the third half hour and perspiration occurred only at the end of the test.

As far as can be evaluated from a surface comparison, in these tests the heat loss and the carbon dioxide production agreed in a satisfactory manner.

/174

#### Heat Balance During the Chill Phase

The comparison of heat production and carbon dioxide secretion during the phase of increasing temperatures is of special interest. If the heat increase is rapid, then in addition to the subjective chill sensation there exist also phenomena which clearly show that the heat loss is smaller than normal. The peripheral arteries are contracted and the skin is white, cool and dry. The water evaporation on the surface is restricted to a minimum.

The heat production on the other hand is increased drastically. This not only covers the heat loss but the produced heat also serves to heat up the body of the patient. Since it is possible to easily determine the amount of heat required to heat up the body, then in such cases with a rapid temperature increase it would be possible to determine the heat production of a fever patient approximately.

As I observed during that discussion [8], in an adult, in order to increase the temperature of the body by  $1^{\circ}$  C, as much heat is needed approximately as the person will generate under normal conditions over one-half hour. Therefore, if during the course of half an hour the body temperature increases by  $1^{\circ}$ , then we know that the heat production has exceeded the norm. In order to heat up the body, an amount of heat has been consumed which would correspond to the normal production during this time. In addition, a certain amount has been given off to the outside. In the case of intermittent fever patients which I observed, during the chill stage two and one-half times the normal production was used to heat up the body. If the heat given off to the outside were normal during that time, then one would have to conclude that the heat production had increased to three and a half times. However, during the rapid increase in the body temperature, the heat loss usually is reduced, then in this case one can no longer say with certainty that the heat production had exceeded two and one-half times the normal

production. Of necessity, it would have to be between two and one-half times and three and one-half times.

/175

During this time, what is the carbon dioxide secretion during this excessive phase of heat production? Has it also risen by this enormous ratio? Or does this enormously increased heat production not correspond to such an increase in carbon dioxide secretion? This would be thinkable a priori because one could assume that the enormously increased oxidation processes would not continue up to the end products at the same time, or that the formed carbon dioxide would not be secreted at the same time.

The previous experiments gave some indications. The greatest carbon dioxide secretion always occurred time intervals where the temperature was still increasing. But the temperature increase occurred during the observation time only very slowly, and the increase in the carbon dioxide level in the first patient (second series, first half hour) was only 30 to 43%. In the second patient (second series, third first half hour) the increase was only 32%. Therefore, this increase is not at all as large.

We obtained unambiguous results by exact observation of the temperature variation in the carbon dioxide secretion during the entire course of the chill phase. These observations were performed in such a manner that the patient was introduced to the apparatus sometime before the expected attack. First only the variation of the carbon dioxide secretion was investigated during the feverless phase. Immediately afterwards and without interruption, this was done during the chill phase and also partly during the heating phase. The attacks were not especially severe but the chill had developed clearly. Shaking was only moderate.

3. The patient (Baumlin) was 41 years old and small and weighed 54.5 kg. He was afflicted with febris intermittens quotidiana (intermittent fever). Later on the attacks were completely eliminated with one gram of quinine.

The first observation (heat table II) was made on the afternoon of April 15, 1870. In addition to the carbon dioxide production for the individual time period, I also give the body temperature (armpit) for comparison at the end of each individual time interval. I also give the difference which the same experienced during this time interval. Finally, I give the ventilation magnitude of the apparatus during the individual time periods, which is important for later

/176

exact calculation.

	Body tem- perature at end of time period	Increase in tem- perature during the time interval	Secreted carbon di- oxide in grams	Ventilation of appara- tus in liters
In the 1st half hour	36.9	0.1	13.85	920.2
2nd	37.55	0.65	20.12	913.3
3rd	39.45	1.9	34.20	891.4
4th	39.85	0.4	19.31	899.9
5th	39.85	0.0	17.68	903.6
6th	39.85	0.0	16.75	921.3

The result of this observation series is remarkable. We can see how the carbon dioxide production slowly arises already during the second half-hour by about 45% while the body temperature increases slowly. In the third half-hour there is a rapid increase in the body temperature and an increase in the carbon dioxide by 147%. The enormous amount of 34.2 grams is secreted in one-half hour. During the 4th time interval, the temperature increases even more, but the increase is only slow. Correspondingly, the carbon dioxide secretion decreases and exceeds the norm only by 39%. Finally, in the two final half-hours where the temperature remains close to 40° and constant, the carbon dioxide secretion is only 28% or 21% higher than during the first half hour, respectively.

During the fast increase in the temperature during the third half-hour, almost twice the amount of heat was used to heat the body, compared to what is used under ordinary conditions. Production not only had to deliver this heat but also had to cover the reduced heat output to the outside. The carbon dioxide production was 2-1/2 times the normal level.

4. A second observation series was made with the same patient on the afternoon of April 18 (see table III). Two half-hours passed before there was a substantial increase in temperature. At the time of the fastest increase during the fourth half-hour, the carbon dioxide secretion was determined separately for each quarter hour.

	Body temperature at end of time interval	Increase in temperature during the time period	Secreted carbon dioxide in grams	Ventilation of apparatus in liters
In the 1st half hour	37.0	0.05	13.00	984.7
2nd	37.1	0.1	13.77	985.6
3rd	37.75	0.65	20.59	986.6
4th	39.4	1.65	31.07	977.9
5th	39.9	0.5	18.09	970.6
6th	40.2	0.3	19.42	990.7

The results correspond exactly to the previous observation. First of all, I would like to emphasize that again during the time intervals where there was a fast heating up of the body, there was an enormous increase in the heat production. The carbon dioxide secretion had risen by the same enormous ratio. In one-half hour, 31 grams or almost two and one-half times the normal amount was secreted.

These observations complete the summary about the variation of the carbon dioxide secretion during the individual phases of intermittent fever attacks. First, they show, just like in previous reports, that the carbon dioxide production depends only very slightly from the absolute level of body temperature. At the time when the patient temperature was stationary at almost  $40^{\circ}$ , the carbon dioxide production was greater than during the normal state, but only about half as great as during the time intervals with low temperature but temperatures which were increasing rapidly. A comparison of the test results with available data show that there is the same good agreement between the observed changes in the carbon dioxide secretion and the assumed changes in the heat production as in the earlier tests.

All of the tests, therefore, contributed to the formulation of the theorem that carbon dioxide secretion during all phases is approximately proportional to heat production.

For an exact comparison, it is appropriate to graphically plot the body temperature and carbon dioxide production. Several special features will then become clear and at the same time certain errors in the results can be improved.

Plates II and III show the temperature and carbon dioxide observations during the last two tests (3 and 4).\* The solid curve shows the temperature variation. The directly read-off numbers are given by dots. The readings were only taken during 8 minutes and only tenths of a temperature degree were taken into account. This means that the points can be somewhat large. Where continuity was required for the curve; it only had to touch the points without always passing through the center of the points.

/178.

The values for carbon dioxide during the individual time phases is first represented by rectangular shaded boxes with horizontal shading. The number on the top gives the amount of carbon dioxide measured for the time interval in question in grams.

However, these shaded areas which have perpendicular rising or dropping boundaries do not give a complete picture of the variation of carbon dioxide secretion. This is because the transition from small production to high production levels, and vice versa, occurred not only discontinuously but gradually. Therefore, the boundary of the areas representing the carbon dioxide secretion should not be a broken line but a continuous curve. It would not be difficult to construct it. It would only have to be subjected to the condition that the limited areas would have to correspond to each individual time interval, just like the rectangular areas of the observed amounts of carbon dioxide.

The construction of such a curve is of special interest. All of the previously indicated carbon dioxide values given as horizontally shaded areas in the plates have been calculated with the simple formula III (Article I, this Archive, Vol. VII, P. 82). As already discussed in the derivation, this formula only gives exact values if during the individually calculated time intervals the level of carbon dioxide production was the same. If there are substantial increases or decreases in the intensity during individual time intervals, then the value obtained must be corrected if one wants to obtain completely accurate results. This is done according to another formula given previously (l.c. p. 85-87) or in other appropriate formula.

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\*Translator's note: Plates missing from German text.

Therefore, we had the problem of improving the continuous curve by means of an exact calculation and correcting the errors in the result. This made the task very complicated and difficult. The individual curve segments had to be calculated so that the limiting areas corresponded to the exact amounts of carbon dioxide. In addition, the individual segments had to be pieced together in an approximately continuous overall curve. After several attempts, I was finally able to solve the task of generating both curves with sufficient approximation.

The position of the curve was calculated for every five minutes and is given by dots in the plates by small points. The surfaces with vertical shading limited by the continuous curve therefore represent the exact calculated values for carbon dioxide production during the individual time intervals. These exact values are given on the upper horizontal lines for the individual half hours. As can be seen, these are smaller with increasing production and are larger for decreasing production than the results of the simple calculation. However, the deviations are not very large.

/179

A certain amount of tolerance was available for the curve. The conditions to which the curve had to be subjected are so complicated that the degree of arbitrariness is very severely restricted. For example, the maximum can be somewhat more pointed (Plate II) or flatter (Plate III), but the point where the maximum occurs can be displaced only by a few minutes either forwards or backwards without making the solution of the task impossible. The exact numbers which result for the production would not be much different for any other curves if the conditions are actually satisfied. In any case, these numbers are much closer to the true values than the ones obtained by the simple calculation. Any deviations probably are more due to experimental errors (see first article) than due to the calculation.

In my discussion of the calculation, I give some special data which are sufficient to recalculate the ventilation using the quantities given above. The volume of the ventilated space in the first experiment was 1117 liters, and 1122. liters in the second one. In all calculations, the time intervals were divided up into intervals of one minute each. In Plate II, the production was assumed to be constant for the first time interval and then assumed to be accelerated during the second time interval (formula VI). In the third half hour a maximum was assumed in the 12th minute, around which the production is grouped, both during

the increasing phase and the decreasing phase in an approximately uniform manner over 18 minutes. The first 12 minutes were calculated according to formula VII and the last 18 minutes were calculated according to formula VI. During the 4th time interval, the first quarter hour was calculated with formula VII and the 2nd quarter hour and the following time interval were calculated using formula V. The curve was assumed to be linear starting at the center of the 4th time interval. In the 5th and 6th time interval, it was assumed that the curve intersected the horizontal boundaries obtained during the first calculation in the center. In Plate III for the first half hour, we assumed uniform intensity and for the second half-hour, uniform increase (formula V). During the third half-hour we assumed accelerated increase (formula VII). During the fourth half-hour where there are two determinations, we assumed a maximum during the 10th minute and the calculations were done with formula VII during an increase with a reduced rate of increase. It was assumed that the production between the 6th and 10th minute was equal to that of during the 11th to 15th minute. Then during the first quarter hour of the excess in production at the end of the third half hour,  $77/128$  of this amount falls on the first 10 minutes, as the calculation shows. The other five minutes were calculated with formula VI, as was the following quarter hour. During the fifth half hour, we assumed a reduced increase according to formula VII during the first quarter hour and the production was assumed to be constant for the second quarter hour. The deficit of the production during this half hour below the level at the end of the previous time interval is divided into  $31/76$  for the first quarter hour and  $45/76$  to the second quarter hour. In the sixth half hour, formula VI was used.

If we compare the carbon dioxide production and body temperature curves (Plates II and III), we can immediately see that these increase together but there is neither parallelism nor proportionality. The maxima of both curves do not coincide at all. The carbon dioxide curve dropped again but the temperature curve continued to increase. /180

This was expected. If one were to show the intensity of solar heat by a curve, and another curve were to show the temperature of air of the ground, then the same condition would exist. The effect of the sun has its daily maximum at noon and its yearly maximum occurs on the longest day of the year. But the maximum of temperature does not coincide with it, but occurs later on. The temperature continues to rise even though the solar intensity is decreasing. But another

condition is noticeable: the temperature increases most rapidly at the time of maximum solar intensity. After this, the temperature continues to increase for a time but with a decrease in rate.

The same must be true for our curves. If the heat production or carbon dioxide production is increased, then of necessity\* the body temperature must increase. The temperature increase must be more rapid as the heat production increases. The temperature curve must increase most steeply at the point where the heat production is most intensive. However, when heat production starts to decrease again, then the temperature will not immediately drop but will continue to increase as long as the heat production is in excess of the norm (or more accurately, the loss) but its increase must be at an ever-decreasing rate and the curve must become less and less steep.

All the details of our curves correspond to these assumptions. One can easily convince oneself of this by comparing the temperature curve with a ruler. As the carbon dioxide curve increases, the temperature curve also starts to increase and becomes more rapid the higher the carbon dioxide curve is. Almost exactly at the point where the carbon dioxide production reaches a maximum, the temperature is the steepest. After this, it will continue to increase but its steepness decreases continuously: At the point of the carbon dioxide maximum, the temperature curve has a so-called inflection point. The curve has been convex downwards up to this point and changes its character here and becomes concave upward. In Plate III there is a second inflection point at the end of the fifth half hour of the temperature curve. The curve again becomes convex downwards. In other words, the speed of increase which had decreased continuously up to this point again increases. This second inflection point corresponds to a minimum in the carbon dioxide curve, i.e., a relatively low carbon dioxide production, after which there is again an increase. In the case of the fever attack, there was a slight delay, and there was again an exacerbation after this.

/181

The results given above show that carbon dioxide production is at least approximately proportional to heat production. This is even true for the very substantial fluctuations in the variables. The degree of this approximation can-

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\*We will not consider fluctuations in the heat loss here for the time being.

not yet be found from the above discussion. We require an even more exact comparison. We require especially an analysis of the factor which expresses the relationship between heat production and carbon dioxide production.

A result which would show that there was an approximate proportionality between the expelled carbon dioxide and the produced heat would probably be very important for all metabolism investigations. This would mean that carbon dioxide would be a convenient and reliable measure for the total metabolism and heat production. We certainly agree that one can doubt the existence of such a constant ratio. Materials which are subjected to oxidation within the human body have different chemical compositions. The relative amounts for oxidation are not always the same. There is a large difference between healthy human beings with good nutrition where one-half of the nutrition consists of carbohydrates, and a hungry person which only oxidizes body components. In order to solve this question, we must discuss the conditions in more detail. We will find the conditions under which there is exact proportionality between carbon dioxide production and heat production. In addition, we will obtain the factor which expresses this ratio.

In order to derive this factor, we apparently cannot consider the heat of combustion of pure carbon, because in the human body only carbon is oxidized in many compounds. For this reason, already Moritz Traube [9] gave the following useful suggestion: in certain metabolism calculations, one does not use the combustion heat of pure carbon but a higher number. In addition, when establishing this factor, one must also consider other observations in addition to the formation of carbon dioxide, and the water formation must be considered as well. /182

The simplest way of obtaining this factor and to evaluate its importance consists of comparing the simple nutrients which are involved during the oxidation of carbon dioxide, and to compare the heat of formation. The factor which gives the number of heat units (kilocalories) per one gram of produced carbon dioxide will be called C in general. The special factor for substances containing albumin will be called Ce. For fats, it will be called Cf, and for carbohydrates it will be called Ck.

Frankland [10] won acclaim by determining the combustion heat of most of the conventional foods. Albuminlike substances could only be considered in the

analysis since that time. Unfortunately, the evaluation of the results is made more difficult for many scientific purposes. This is because only the raw foods were investigated and only the water content was determined. Otherwise, it was not determined how the individual components are represented in them. For example, if the combustion heat of potatoes, apples, milk, butter, beer types and cheese types, etc. are given, then if the compositions of these substances are obtained, it is not known what was investigated.

In the following collection I have introduced three groups of organic foods with a somewhat constant composition. I give the carbon content, the amount of carbon dioxide produced by the combustion of one gram as well as the combustion heat given by Frankland, and finally the number of heat units per one gram of carbon dioxide. One of the difficult points is the assumption about the carbon content which has not been exactly determined for any of the substances investigated. Even for beef muscle and albumin, where they were washed repeatedly with ether, these are not chemically pure albumin substances. Both still contain organic components and even the former contains glutenous tissue. I have assumed that all the selected substances were chemically pure because this is a comparison. In the case of the nitrogen gas-containing substances, we assumed oxidation to be urea, water and carbon dioxide for the combustion heat and for the carbon dioxide.

Carbon dioxide in percent	Carbon dioxide from 1 gram	Calories from 1 g	Calories per gram of carbon dioxide
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1. Foods containing nitrogen:

Beef muscle	54.9	1.76	4.368	2.48
Albumin	53.4	1.71	4.263	2.49
Gluten	49.3	1.52	3.655	2.40
			Ce =	2.46

2. Fats:

Beef fat	77	2.82	9.069	3.22
Cod liver oil	77	2.82	9.107	3.23

3. Carbohydrates:

Cane sugar	42.1	1.54	3.348	2.17
Commercial dextrose	36.4	1.34	3.277	2.45
Arrowroot	44.4	1.63	3.912	2.40
			Ck =	2.34

These numbers first indicate that the ratio of the carbon dioxide and heat is almost constant for foods in the same group. The question of whether it is possible to calculate the heat production from the amount of excreted carbon dioxide can be affirmed for the case where we know approximately the ratio of the individual groups of nutrients in the total oxidation.

The above numbers are only relative values. For most of them it can be shown that they are too small. For our purposes they can only be used if they were absolutely correct, at least approximately.

According to the excellent work of Favre and Silbermann [11], we have good data for fat. According to the combustion heat of the higher terms in the fatty acid theory, we obtain the desired factor of  $C_f = 3.5$  for the fats.

For carbohydrates, no direct investigations have been made in addition to those of Frankland. However, we can indirectly determine the combustion heat with sufficient accuracy using a calculation which has been done many times since Helmholtz\*. Alcohol produced from one gram of cane sugar according to Favre and Silbermann give 3.86 calories during combustion. In addition, there is also the amount of heat which is formed during the conversion of sugar and alcohol. According to the investigations of Dubrunfaut [12], it is 0.14 per 1 gram of sugar. The combustion heat of cane sugar then, in reality, is about 4.0 calories. This

/184

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\*S. Helmholtz, article and title "Heat" in the Encyclopaedia of Medical Science, Vol. 35, Berlin, 1846, p. 547. Ludwig (Handbook, 2nd Ed., Vol. II, p. 738) has obtained a number when calculating dextrose which was also assumed by other authors. However, it is much too large because instead of the combustion heat of conventional alcohol, the combustion heat of amy1 alcohol was used. Recently, Liebig (about fermentation, the source of muscular force and nutrition. Separate print from the session reports of the Imperial Bavarian Academy of Sciences, 1869, II, 4.) derived a theorem from a similar calculation and assumed that the Frank Frankland number was exact. It is directly in contradiction with the axiom that the force is constant. One has no other choice but to either assume that the Frankland number for cane sugar is too small or to assume that the *perpetuum mobile* has been proven. This choice should not be a difficult one.

means that the factor for carbohydrates would  $C_k = 2.6.*$

All determinations so far have been lacking for albumin substances. This means that the Frankland numbers cannot be checked. However, indirectly, it can be shown that for these compounds the combustion heat is substantially higher than he found.

If we fix the ratio of heat production and carbon dioxide production for fats and carbohydrates, then it can be determined for albumin — containing substances by simultaneous investigation of heat and carbon dioxide production of an animal for which the nutrition pattern is approximately known. A large number of such investigations have been made by Dulong [13] and Despretz [14]. However, the reliability of the absolute numerical values are open to question.\*\* The relative results, however, seem to be very reliable considering the care with which the investigation was performed and the exact agreement between both observers. We will use these relative results.

Both observers reached the conclusion that more produced and directly determined heat is covered in the plant-eating animals because of the carbon dioxide burning, compared with meat-eating animals. For the same heat production, the ratio of the carbon dioxide production of meat-eating mammals\*\*\* to that of plant-eating animals is 1 : 1.26 according to Despretz and it is 1 : 1.28 for Dulong. Such a difference between meat-eating and plant-eating animals can only be caused by the differences in quality of the converted material. And since we have the factors  $C_f$  and  $C_k$  for fat and carbohydrates, from those results we could calculate the factor for albumin substances  $C_e$  if we knew the exact composition of the foods of the investigated animals. Only indications of this have been made by observers, so a large amount of flexibility is offered here. I carried out the calculation using generally accepted assumptions. The final result was always about the same. /185

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\*Moritz Traube (Virchow's Archives, Vol. 21, p. 417) assumes that the heat produced during fermentation is 0.152 calories according to actual data per gram of Amylum. He calculates the combustion heat of starch flour to be 4.232. This number agrees exactly with the number assumed above. It results in a factor of  $C_k = 2.6$ .

\*\*The carbon dioxide values obtained by Despretz all seem to be too low. Despretz himself assumes a loss due to absorption by water of the gasometer and, therefore, constructed his mercury gasometer which was not used during these investigations.

\*\*\*We only consider mammals, because during oxidation of albumin into urea, the factor is somewhat different.

The Frankland number cannot be reconciled with the results of Dulong and Despretz. Under these conditions, the combustion heat of albumin must be greater in such a manner that the factor Ce must be much closer to the factor for fats Cf, compared with the factor for carbohydrates Ck.

In order to demonstrate the narrow limits within which the result varies for various assumptions, let us, for example, use the average number of both observers, according to which the carbon dioxide production of the meat-eating animal to that of the plant-eating animal is 1 : 1.27 for the same produced amounts of heat. Then the factor Ce which expresses the overall ratio of heat to carbon dioxide must stand in an inverse proportion for both groups of animals. Let us call percentage of the albumin substances among the substances oxidized by the plant-eating animals by E. Let us assume that it is F for fats and K for carbohydrates. For the meat-eating animals we will use the corresponding quantities E' and F'. We then obtain the following equation:

$$1:1.27 = E.Ce + F.Cf + K.Ck : E'.Ce' + F'.Cf'$$

By introducing the well-known values of Cf and Ck, we have:

$$Ce = \frac{F \cdot 4,415 + K \cdot 3,302 - F' \cdot 3,5}{E + E' \cdot 1.27}$$

We will now assume for the time being the following average percentage: E = 13, F = 3, K = 84, for the oxidized materials of the plant-eating animals (rabbits and guinea pigs). For the meat-eating animals (dogs and cats) we will first make the extreme assumption that at the time of the experiment they have oxidized three times as much fat as albumin substances. We then obtain Ce = 3.3. If they had oxidized twice as much fat as albumin, then we would have Ce = 3.4. If equal amounts of fat and albumin had been converted, then we would have Ce = 3.45. If we assume less fat than we obtain Ce = 3.47, if the fat-to-meat ratio is 1 : 2. If it is 1 : 4, we obtain Ce = 3.48. For less fat, Ce does not become much larger. This means that for any possible assumption, the factor Ce is between 3.3 and 3.48. /186

If for the metabolism of plant-eaters, we had assumed more fat, then the factor Ce would have been inconsequentially larger. If we assumed less fat, then it would have become somewhat smaller. For example, if we made the extreme assumption that the plant-eating animals had no fat at all at the time of the test, and that they had oxidized 10% of albumin and 90% of carbohydrates, then we would find

$Ce = 3.3$  if the meat-eaters convert the same amount of fat and albumin. If the latter convert larger amounts of albumin, then  $Ce$  would approach the value of 3.4 without exceeding it.

According to these comparisons, we can no longer doubt the fact that the ratio of heat to carbon dioxide during the oxidation of albumin substances in the bodies of mammals must be greater than found from the Frankland determinations of the combustion heat, the factor of 2.46. Nevertheless, it is not appropriate to derive a certain number from the data given. This could only be done if the relative results of Despretz and Dulong were considered completely accurate, and if in addition the corresponding factors for fats and carbohydrates were determined with absolute certainty. The factor  $Ce$  would increase and decrease just like the factor  $Ck$ . In contrast to this,  $Ce$  depends in an inverse fashion on  $Cf$ .\*

If we assume that the Frankland number is too low by the proportion for albumin as was the case for cane sugar, then the albumin factor would then increase to 3.0. If the investigated albumin were chemically less pure than the investigated cane sugar, or if it were burned less completely, then it could be assumed to be even somewhat higher. These assumptions are certainly possible considering the properties of albumin. According to the coincident results of Despretz and Dulong, it should be between 3.3 and 3.5. If we assume 3.3, then this number seems to be somewhat too small. From this we could calculate the combustion heat of chemically pure albumen in the body of mammals to be 5.6.

According to this discussion, per one gram of produced carbon dioxide, we have the following:

For fats	3.5 Cal. —	$Cf = 3.5$
For albumin substances	3.3 "	$Ce = 3.3$
For carbohydrates	2.6 "	$Ck = 2.6$

Therefore, for human beings the factor which gives the ratio of the heat production and carbon dioxide production must lie between the limits 2.6 and 3.5 under all conditions. If we know the type of nutrition or the ratio of the materi-

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\*Even if we set  $Cf = 3.6$ , which would be the extreme outer limit, then by assuming equal amounts of fat and meat, we would obtain  $Ce = 3.3$  for the meat-eating animal.

als subjected to oxidation; the heat production can be calculated from the observed carbon dioxide production. Even if this ratio is not exactly known but is only approximately known, sufficient accuracy can be achieved. Even substantial errors about the relative amounts of oxidized substances only have a small influence on the average value of C which results. Any errors in the determination of the ratio of the fats and the albumin substances would become almost unnoticeable. Changes in the ratio of both with respect to carbohydrates only result in very slight fluctuations. For example if in humans the ratio of converted fats, albumin substances and carbohydrates were 1 : 1 : 1, then the factor of C = 3.1 would result. If the ratio were 1 : 1 : 2, then C = 3.0. If the ratio were 1 : 1 : 3 or 1 : 1 : 4, then we would find C = 2.9. For a healthy human being with good nutrition, the factor C will always amount to about 3.0. The less carbohydrates consumed, the greater will be the likelihood that this number will be exceeded. The greater the supply of carbohydrates, the greater will be the tendency for the number to drop below this number. As the investigations of Regnault and Reiset have shown, this would occur soon after consumption of the carbohydrates. A maximum would be reached for exclusive fat diets or for fat and meat diets, as for abstinence from all nutrition, in which case the body consumes its own fat and meat. The factor would then be between 3.3 and 3.5. In any case, the limits are narrower enough to be able to consider the factor approximately constant for time intervals with approximately the same nutrition conditions.

A calculation by Helmholtz is an important check on these calculations. This author wrote a classical article called "Heat" in the Encyclopaedia Handbook [15]. He made the attempt to numerically determine the heat production of a healthy person. He used calorimetric investigations on animals of Dulong. He carried out the same investigation on humans. He also considered the carbon dioxide investigation and water formation investigation of Scharling and Valentin. The value obtained for an 82 kg body weight human agreed very well with all later experiments and is justifiably used as a normal number in comparisons. It can easily be reduced to any other body weight, using the Immermann formula [16]. From the same data, we can determine the ratio of heat production in carbon dioxide secretion for healthy humans, using the same combination used by Helmholtz.

It is found that when one gram of carbon dioxide is secreted, this corresponds to a heat production of 3.1 calories, which is almost exactly the same number as we found in another way.

/187

/188

In the case of a fever patient, one must consider the fact that at least for a severe fever attack, he will oxidize part of his own body substance. Therefore, a somewhat higher average value for the factor C must be used. We will assume 3.2 calories per gram of carbon dioxide. The approximate calculation of heat production then gives an idea about the entire heat balance in a fever patient.

As long as the body temperature increases, a part of the produced heat is used to heat up the body. This part is found from the observed temperature increase.

The remainder is the amount of heat given off to the outside.

However, we have not considered the fact that the temperature increase is not the same for all body parts. According to experience, the body surface and the peripheral parts are heated up somewhat later on than are the inner parts. If for our case we assume that the temperature increase occurs one-quarter of an hour later for the fifth part of the body, than for the armpit, then we obtain the numbers in parentheses given in the last column of the following table. These are probably closer to reality than if we had not considered this factor.

For the third experiment (page 176, Plate II), we obtained the following values (the body weight of the patient was 54.5 kg., the average heat capacity of the body is assumed to be 0.83):

	Increase in body temperature	Carbon dioxide production	Heat production	Used for heating the body	Heat output to the outside
In the 1st half hour	0.1	13.85	44	5	39 (41)
" 2nd " "	0.65	19.07	61	29	32 (34)
" 3rd " "	1.9	34.49	110	86	24 (29)
" 4th " "	0.4	19.50	62	18	44 (38)
" 5th " "	0.0	17.99	58	0	58 (57)
" 6th " "	0.0	17.15	55	0	55 (55)
In 3 hours	3.05	122.05	390	138	252

The fourth experiment (Plate III) gives the following numbers:

/189

	Increase in body temperature	Carbon dioxide production	Heat production	Used for heating the body	Heat output to the outside
In the 1st half hour	0.05	13.00	42	2	40 (40)
" 2nd "	0.1	13.67	44	5	39 (40)
" 3rd "	0.65	19.48	62	29	33 (36)
" 4th "	1.65	31.44	101	75	26 (28)
" 5th "	0.5	18.32	59	23	36 (31)
" 6th "	0.3	19.07	61	14	47 (48)
In 3 hours	3.25	114.98	369	148	221

The numbers in the last column are calculated from those of the previous column. They have the least absolute accuracy, because they contain the observational errors as well as the errors about the assumptions. Therefore, one can test the validity of the observations and the assumptions using them.

First the agreement of both observational periods is very good if we consider the fact that the second fever case occurred somewhat later and was of longer duration. In addition, the values obtained for heat loss for the individual time intervals agree very well with the conclusions which can be drawn.

The normal average heat production of a human being weighing 54.5 kg would about 43-1/2 calories according to the Helmholtz number and using the Immermann formula, per one-half hour. The heat would be the same under normal conditions. In both test periods for the heat output at the time where the temperature was still within the normal limits, we found a somewhat lower value. This was to be expected for the time period of apraxia in a fever patient who had already experienced many attacks of intermittent fever. In both test periods, the heat output at the time when the body temperature increases, during the chill phase, has dropped below the norm, which agrees completely with what was discussed above. It reaches the lowest value at the time where there is the most rapid increase in body temperature. Finally, when the constant temperature is reached which does not yet rise very much, the heat loss then exceeds the norm.

This means that the results of this exact comparison agree in all details

/190

with everything that was known about these conditions. This analysis gives an overview about the variation of the carbon dioxide, heat production and heat output during the chill stage and the heating stage of an intermittent fever patient.

This agreement at the same time gives a certain guarantee for the correctness of the assumptions used for the calculations. For example, we can conclude that our number for the average capacity of the human body and the factor for determining the heat production from the carbon dioxide production is probably not very far from the real conditions. It is also found, which was dubious to begin with, that the produced carbon dioxide is excreted at approximately the same time during which there is an increase in the heat production due to the increase of the armpit temperature.

Finally, this coincidence of the results shows that our assumption of a constant ratio between carbon dioxide production and heat production during fever is approximately correct. Accordingly, carbon dioxide is a reliable measure for total metabolism. *A priori*, we can assume that certain special circumstances and the different qualities of the converted materials will result in deviations from this. However, these deviations seem to be very small and do not seem to influence the results. These results were an attempt to obtain the first information about this area of research. For the time being, they lie within the error limits.

#### The Theory of Fever

The previous discussion and experience has shown that the ratios of body temperature, heat production and carbon dioxide production can be accessible to a physical treatment during the individual phases of fever. Sufficient knowledge about these individual processes and their physical composition can be obtained.

We found that the increase in the body temperature during fever is caused primarily by an increased heat production. Only during the chill phase with a rapid temperature increase is there also a reduction in the heat loss, which is certainly secondary. In general, one can say that during fever the human body becomes warmer because it produces more heat, just like an oven becomes warmer when the fire in it is stoked up.

Have we reached our goal about the knowledge of these physical processes? And have we obtained a sufficient theory of fever? Is the difference between the heat economy of a fever patient and a healthy person only due to the fact that the fever patient produces more heat? I do not believe that we can answer these questions with a yes.

The previously discussed physical ratios are not sufficient for understanding the heat economy of a fever patient. We must also include a physiological moment.

At the present state of knowledge, we are still very far removed from a real theory of fever. However, strange individual processes during the different phases which were discussed in the previous section require us to go beyond the previously established physical point of view. We must obtain points of view from which these processes can be interrelated with the processes of healthy persons. Such a point of view can be achieved in the physiological area, if we compare the different fever phases with certain usual and unusual phases in healthy persons. First of all, it will not be possible to avoid a more or less teleological method of expression, and I would like to remark that I will use it with the expressed intention of thereby shortening the discussion and to make it more clear. Much can be summarized in a teleological manner, which cannot be understood by causal relationships. In any case, teleology can be at least given the role of an aid for making the discussion clearer and to establish directions of research. Since Darwin, the teleological point of view of organic nature is easily translated into a causal point of view. For any science, it seems to be justified. /192

A comparison of the various fever cases with certain states in healthy human beings seems to give one important result, even though it is deficient in many respects. The heat economy of a fever patient is the same as in a healthy person under all conditions. All of the many deviations between the fever patient and the healthy person can be attributed to a single factor for the most part.

Let us start with the phase where the conditions are simpler, the heating phase. During this phase, the heat production and the heat loss are in equilibrium, as mentioned above. This phase corresponds to the normal state in human

beings. The difference is only due to the fact that the fever patient reaches an equilibrium state at a temperature of about  $40^{\circ}$ . In healthy persons it is reached at a temperature of about  $37^{\circ}$ .

In the fever patient at this time the heat production is about 20 to 25% greater than in a healthy person. Because of this increased heat production, he is capable of maintaining his body temperature about three degrees higher for the same conditions in the surroundings.

Very often the heat production in normal human beings is increased just as much over a long time period.\* A human being with good digestion could bring about such an increase by a continuous supply of rich food. It always occurs during intensive muscular work. The degree of stress is so low for an increase between 20 and 25% that it can easily be maintained over a whole day without interruption. The body temperature is much different than in a fever patient. It increases only by a few fractions of a degree. Even for long duration stress, a febrile temperature was never reached. In order to make everything the same, if one were to bring the body temperature to  $40^{\circ}$  in an artificial manner, for example, in a bath, then with continuous exertion it would not remain at this level, but instead would very soon return to the normal level. /193

If the body temperature of a healthy person is increased artificially, then a few cold rinses are sufficient to bring about their normal temperature again rapidly. In fever patients, this first of all does not result in any noticeable decrease of the very high temperature.\*\*

These simple facts show that the difference in the behavior of a healthy person and the fever patient does not only consist of the difference in heat production but that there is something else.

The healthy person has the tendency to maintain his normal temperature at

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\*For short time intervals, the heat production of healthy persons can reach levels such have never been observed for fever patients. During experiments made in 1866 in collaboration with Prof. C. E. E. Hoffmann it was found that during intensive work, for example, climbing mountains, the heat production for short time intervals is increased to four times the normal production and even more. The simultaneously performed mechanical work was not included in the analysis.

\*\*See the medical clinic in Basel. Leipzig, 1868, p. 91 ff.

about  $37^{\circ}$ . He very effectively defends himself against cooling and heating. If the temperature is abruptly changed in any manner, he will return to the normal temperature as quickly as possible. The fever patient has the same intention of maintaining his temperature. However, he will stick to the very high temperature of  $40^{\circ}$  if it is possible for him to do so. If the temperature is drastically changed, he will return to this temperature nevertheless as quickly as possible.

In spite of the many changes in the external and internal conditions, he is capable of maintaining his normal temperature because of the very complex physiological processes. Part of them are sufficiently well-known and physically understandable. Others can only be demonstrated as to their effects without knowing the mechanism. We only have rough ideas of these mechanisms. The performance of this entire apparatus is called heat regulation.

The heat regulation first consists of a regulation of the heat loss. If the human body is subjected to conditions which facilitate heat loss, for example if he is naked in the cold air or jumps into cold water, then there will first be a cooling of the skin surface. The colder the surface becomes, the less heat will be expelled to the outside. In addition to this factor which would occur in the same manner in any dead body, the contracting elements of the skin and the surface vessels are set into action. This restricts the circulation in the skin and the heat supply from the inner organs. This condition and the additionally retarded water evaporation represent an effective protection against excessive cooling. Because of the cold sensation, we are also led to use any means for restricting the loss. This includes selecting the position of the body, the body posture, clothing, quarters, heating, etc. If, on the other hand, the external conditions make heat expulsion more difficult, for example if the surrounding is relatively hot, then there are other methods of counteracting this, so that the heat loss can nevertheless be maintained at the normal level. The skin and its vessels become limp. The blood circulation to the body surface and therefore the heat supply is intensified. The surface gives relatively more heat to the outside due to this. The skin becomes wetter or starts to perspire and the increased water evaporation means that the heat loss becomes much larger, i.e., when the surrounding air is relatively dry and is somewhat in motion. The heat loss is greater than would correspond to the existing temperature difference. In relatively dry air, the human being can exist at a temperature which is as high as the body temperature or even higher. In the experiments of the English observers of 1775,

an air temperature was withstood which even reached or exceeded the boiling point of water for a short time.

All of these devices for regulating the heat loss would suffice at the most under especially favorable or relatively slowly changing conditions, in order to maintain a constant body temperature. They become insufficient for large fluctuations in external conditions. The healthy person will maintain a constant temperature for a certain time when he is immersed in cold water. In spite of all the regulations of the heat loss, actually more than four times the heat is withdrawn as would occur under usual conditions. Under such conditions, the temperature can only be maintained constant because the heat production is increased by an appropriate ratio. In addition to the regulation of the heat loss, we also /195 find a regulation of the heat production after heat loss. The experiments which Kernig and I performed\* where the quantity of the expelled heat was determined directly and the amount of heat production was established showed that this regulation of heat production occurs over a very wide range in healthy persons. For example, in a 34° - 35° bath the heat production is approximately according to the norm. In a 30° bath it is increased to twice the amount. In a 24° bath it is tripled, and in a 20° bath it is four times the normal production.

What happens to a fever patient? Is there a heat regulation involved?

Since the higher temperature of a fever patient already shows that the conditions are no longer normal for him, one has usually made the assumption that there was no regulation at all. However, a number of facts show that in fever patients the heat regulation is less productive but nevertheless operates exactly the same as in a healthy person. However, in the fever patient it is not a normal temperature but a certain higher temperature which is being regulated.

We can demonstrate the fact that there is a regulation of the heat loss in the fever patient from the fact that he will decide for an appropriate cover just like a healthy person, using his subjective sensation of cold or heat. If large amounts of heat are removed, for example in the cold bath, then the same mechan-

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\*Reichert's and du Bois-Reymond's Archive, 1960, p. 589 ff. Kernig experimental contribution to the knowledge of heat regulation in humans. Dorpat 1864. See this archive, Vol. V, p. 217.

isms are involved as in healthy persons against excessive cooling. As discussed earlier, it is clear that the contraction of the skin and its vessels is not as intensive. Therefore, the protection against the cooling is of lesser importance than in a healthy person.

In the fever patient there is also the regulation of the heat production after heat loss, as numerous calorimetric tests have shown directly [17]. In a /196  
20° - 22° bath, the fever patient produces more than twice as much heat as in a 34° - 35° bath. However, one finds that his mechanisms are more restricted than for a healthy person. He is capable of resisting the cooling for shorter time periods.

Accordingly, we can see that the fever patient will energetically maintain his temperature of around 40°, if he has the means available, just like a healthy person maintains a temperature of 37°. The heat production changes within wide limits for a fever patient. It increases or becomes smaller, as required for purposes of maintaining a certain temperature. Under certain conditions, the heat production of a healthy person can be greater than for a fever patient. However, the healthy person can increase his heat production by exertion and regulates to a lower temperature. He then opens the path for a heat loss so much that his temperature never reaches the temperature of a fever patient, even though his heat production may be much larger.

The most important difference between the healthy person and the fever patient, therefore, is in the magnitude of heat production. Under usual conditions, it is greater for a fever patient than in healthy persons, because this is a physical necessity so that he can maintain a higher temperature. The most important difference is in the temperature level at which both regulate the heat loss and the heat production. The fever patient has a higher temperature because he produces more heat. From a physiological point of view, it would be more correct to say he produces more heat so that he can maintain a higher temperature. Fever not only includes the increased heat production, but as I already mentioned earlier, the existence of a tendency to maintain an abnormally high temperature. In other words, this is the regulation at a higher temperature level.\*

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\*Cited work, p. 130.

I do not know how to summarize the results any briefer than by stating the following: In a fever patient, the heat regulation is regulated to a higher temperature level. However, I do not believe that this is an explanation for the essence of fever. As long as we do not know the details about the wonderful regulation of heat production according to heat loss in healthy persons, we probably will not have a scientific understanding of the pathogenesis of fever. With the assumption of adjustment to a higher temperature level, we have not stated anything about the mechanism of the regulation itself or the adjustment to a certain temperature level. Nor have we clarified the reasons why the various regulations occur. Everybody can have his own hypothesis. Several authors consider nerve actions and central organs. However, this does not have to be discussed here, because it is not important for the preceding nor the further discussion. I will select the term because it does not make any hypothesis nor does it relate to any known facts. However, it clearly expresses the heat regulation at a certain temperature level and is easily understandable.

/197

It is also important to realize that it is not the internal temperature but the temperature of the skin or a certain level below it which is important for heat regulation.

According to this discussion of the heating phase, one can easily understand the behavior of the fever patient during the perspiration phase and can relate it to the behavior of healthy human beings. If the fever decreases rapidly, i.e., if there is heat regulation which previously had regulated to a high level, and if it just as rapidly adjusts to a low level, then the fever patient is in exactly the same condition as a healthy person whose body temperature has been artificially raised. The temperature in both is higher than would correspond to the regulation. Therefore, in both, the locks for heat outflow are opened as much as possible. The expansion of the vessels on the skin surface allows an increased loss due to conduction and radiation. Perspiration occurs and, therefore, there is a strong heat loss due to water evaporation. Often the heat loss is accelerated by avoiding warm clothes, by exciting the air flow, etc. There is only one difference here: in healthy persons, to begin with the regulation is at the normal level and therefore the restoration of the normal temperature is as fast as external conditions permit this. On the other hand, in fever patients, the adjustment is not instantaneous. Instead, it decreases only gradually and often with fluctuations from the earlier higher level to the normal level, and this is

the reason for the long duration of this state.

It is found that the secretion of perspiration which is characteristic for the fever phase depends greatly on the heat regulation for numerous other conditions. We will not discuss in detail the complicated and unclear relationships here. I would only like to point out that in most states, where perspiration secretion is observed, one has the universal empirical rule that there is an expansion of the skin vessels and the secretion of perspiration whenever the temperature of the skin is higher than would correspond to the instantaneous adjustment of the heat regulation. This includes all the conditions which restrict the heat loss of the skin -- for example, increased temperature of the surrounding air, a warm covering of the skin, etc. This also includes conditions which increase the body heat without changing the regulation adjustment, for example, muscular work, large amounts of hot drinks, and similar factors. It is possible that one should also include the very remarkable and difficult to understand conditions during which there is perspiration at an extremely low body temperature, for example, when perspiration occurs during sudden weakness states or unconsciousness indications, during depressions, during collapses, under agony, etc. In any case, the variation of temperature in these cases seems to indicate that a rapid adjustment of regulation to a temperature level has occurred which is lower than the existing skin temperature.\*

The chill phase phenomena are very remarkable and at first glance completely contradictory to other everyday experience. The strongest subjective cold sensations with other indications of serious freezing occur when the body temperature is in the process of a rapid increase. /199

We believe that this contradiction also fits into our point of view, a contradiction which had not been explained up to the present time.

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\*In my investigations about the application of diaphoresis during chronic morbus brightii (Prague Quarterly, Vol. 72), I was able to summarize a great deal of my experience with the following theorem: perspiration is caused by all conditions which make the skin temperature become equal to the temperature inside the body to a certain degree. My observations at the time include those where there was substantial perspiration and the skin temperature of the thorax was greater than that of the closed mouth cavity. It can be seen that this theorem includes the above rule completely. The above rule is more general because it also includes other states and the conditions of a fever attack. At the time, I was not able to reconcile these findings with other experiences.

The state of a fever patient during the chill phase apparently is similar to that of a healthy person who is brought into a cold bath. In both, there is an intense subjective chill sensation, shivering or shaking. There is accelerated short and irregular respiration, etc. The peripheral arteries are contracted, the pulse is low and hard, and the skin muscles and the vessels are energetically contracted. The skin is white and the lips and nails become blue. On the other hand, the degree of heat production achieves a very high level in both. It increases to twice, three times or even more times the normal level. The carbon dioxide is also increased by the same amount.\* We can see that the organism uses all of its available means in both persons to restrict the heat loss as much as possible and to increase the heat production.

Is this similarity of the phenomena a coincidence or external one? or is there a deeper similarity between both states? I believe in the latter. I believe that the common factor for both states and which is the basis for the many phenomena discussed is the fact that the skin temperature is lower than the regulated temperature level.

In the case of a fever attack, the adjustment which was previously at the normal level rapidly increases to a higher level. The skin layer which determines the regulation temperature will first stay normal, i.e., lower than would correspond to the regulation adjustment. Then the regulation occurs in the usual way. This is done by restricting the heat loss as much as possible and by increasing the heat production as much as possible until the temperature level is reached which corresponds to the regulation adjustment. If during this time the regulation temperature is increased successively to ever-higher levels, then the same processes must repeat again, or they must at least continue over a certain time period. The faster the regulation adjustment at the higher level occurs, the more pronounced will be all of the phenomena and the shorter will be their duration.

In the healthy person in a cold bath the regulation remains adjusted at the

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\*The carbon dioxide production is increased to twice or three times the normal production. See the preliminary report about my investigations in Gildemeister, the carbon dioxide production during the application of cold baths and other heat removal phenomena. Inaugural dissertation. Basel 1870.

normal level.\* The temperature of the important skin layer is reduced by the effect of the cold water. This is why there is the same difference between the skin temperature and the regulation adjustment. Therefore, there exists the same amount of effort for restricting the heat loss and there is the same increase in production. There is one remarkable factor which has been noticed by several researchers [18]. Under some conditions due to an increase in the heat loss, the internal temperature in the closed armpit can increase even above the normal level. This can now be explained. The contradictory heat production excess can be explained because of the physical impossibility of making the skin layer temperature approach the required level by increased heat production, as long as heat is removed and without increasing the internal temperature.\*\*

/201

Physically speaking, the fever patient temperature increases rapidly during the chill phase because the heat production increases drastically and the heat loss is reduced. From the physiological point of view, we can reverse this and say the following: the heat production is increased and the heat loss is reduced so that the temperature will reach the level required for regulation as fast as possible.

One objection has not yet been removed: If the heat regulation of a fever patient would adjust very rapidly to a level higher by three or four degrees, then this difference would still not be large enough as in the case of a healthy person whose skin was cooled off by a cold bath. According to our opinion, we would have a bad correlation between the cause and the effect. I believe it is possible

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\*In order to be completely accurate, I must restrict this somewhat. After-effect phenomena show that due to the increased heat loss, the regulation adjustment is also influenced (see publication from the medical clinic in Basel, p. 134 ff). Even after restricting the heat loss or artificially increasing the temperature, this results in a similar after-effect. Since we will first not consider the causes which bring about the various adjustments and since we only wish to explore the conditions approximately, we can ignore these relationships. In a closed theory, on the other hand, it would be very important to establish the dependence between the regulation level and the quantity and quality of material available for the oxidation.

\*\*This internal temperature increase under the given conditions may be substantial unless the increase in heat production would occur very close to the locality experiencing the excessive cooling. This has been demonstrated by Fiedler and Hartenstein (Archive of Health XI, p. 97 ff).

that in addition to what has been said above, there are many other unknown factors here. Their knowledge will explain much about the differences between the fever patient in a chill state and a healthy person in a cold bath. Nevertheless, I do not believe such an assumption is needed at the present time if we consider the fact that the important location for regulation is not located on the outside surface, which certainly is cooled off drastically in a cold bath, but probably is located at a certain depth underneath the skin. I even hope that this deficiency in the correlation in the future will lead to the determination of the location of this layer using physical methods.

Of course, a cold bath is not the only state of a healthy person which can be used to compare with a patient in the chill state. We can make the discussion more general and are then led to the following empirical law for sick persons and healthy persons: If in a human being the skin temperature is lower by a certain amount than the instantaneous adjustment of the heat regulation, then there is a subjective and unpleasant cold sensation,\* a reduction in the circulation at the surface due to contraction of the skin and its vessels, an increase in the heat production and in the carbon dioxide secretion. /202

Here, I will not discuss the possible ways whereby the individual regulation phenomena occur. Most of this belongs to future research. Nevertheless, noticeable beginnings have been made. The previous remarks primarily are intended to give a rough outline of the conditions. Any person who does not wish to go further can be satisfied with the empirical relationship discussed above. It seems to me, for the purposes of research, that it is important to find analogies if none existed before. A summary of heterogeneous facts from a common point of view seems to me to be a type of explanation. A preliminary summary of these complicated and difficult conditions is probably a step in the right direction. A great deal of work will be necessary to formulate a theory which would allow the derivation according to causal points of view and to then derive the phenomena involved. First, researchers will continue the work started above. This will give information about the way in which the central organs influence the heat regulation.

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\*The regulation effect on the chill sensation then becomes clear: It is a warning about arbitrary restriction of the heat loss.

All of the investigations reported so far refer to intermittent fever. I do not believe that these results can be transferred automatically to any other kind of fever. Intermittent fever has always been the representative of fever. The point of view has arisen that intermittent fever is not fever at all, but this is a point of view which hardly can be defended. Statements of older authors like this should also be disbelieved. They simply included intermittent fever in their rational model of the world. They did not have to fear a rebuttal to their theory on fevers which were very difficult to research.

For obvious reasons, it is only rarely possible to observe the chill phase of fever in other illnesses. In the following I will give the results of an observation where this happened to a certain degree. It shows the extraordinary features of intermittent fever attacks and other kinds of fever attacks.

5. A 20-year-old man (Wildy) had abdominal typhoid in our hospital. During his recovery, there is a pleurisy. Even though the pleurisy exudate had, for the most part, disappeared, chill attacks occurred during the early morning hours with moderate intensity and this went along with a substantial temperature increase. Towards evening it was reduced again and complete apraxia prevailed in the night. Large doses of quinine only had intermittent success.

On April 14 the patient was put into the apparatus before a substantial amount of chill had occurred. The observation lasted from 8:15 to 11:45. At the end of the third half-hour, there was slight chilling and a half-hour later light shaking. During the last half hour there was no chilling at all. The body weight was 53 kg and the body length 170 cm.

The results are given in the following table. The same calculation as for the two last observational series were made. We did not carry out a correction because of non-uniform production during the individual time period.

	Temperature at end of time interval	Temperature increase	Carbon dioxide produc- tion	Heat produc- tion	Used to heat the body	Heat ex- change outside
In the 1st half-hour	38.3	0.35	14.9	48	15	33
" 2nd "	38.4	0.1	26.4	84	18	33
" 3rd "	38.7	0.3				33
" 4th "	39.3	0.6	18.4	59	26	33
" 5th "	40.05	0.75	19.2	61	33	28
" 6th "	40.8	0.75	18.4	59	33	26
" 7th "	41.3	0.5	16.7	53	22	31
In 3-1/2 hours		3.35	114.0	364	147	217

The agreement with the conditions of intermittent fever attacks is complete. The large carbon dioxide production occurs the three time intervals with the most rapid temperature increases. On the other hand, during the second and third half-hours during which the temperature increase is the slowest, the carbon dioxide production is also the smallest. During the fourth to sixth half-hour the production is 41% greater than during the second and third half-hour. The temperature is the greatest but increases only slowly, and already starts to decrease again. During the seventh half-hour, it is only 27% higher than during the second and third half-hour.

If one were to construct curves for body temperature and carbon dioxide production, then all of the features would coincide with the curves in Plates II and III. Only there would be a much flatter carbon dioxide curve corresponding to the slower increase curve. The carbon dioxide has a maximum in the fifth half-hour and this corresponds to an inflection point in the temperature curve, which does not coincide exactly with the peak of the carbon dioxide curve but comes somewhat afterwards. This is an irregularity which lies within the error bounds, considering the extended form of the temperature curve and the wide maximum. It is remarkable that in this case the carbon dioxide production also has a minimum during the second half-hour which coincides with an inflection point in the temperature curve. As Plate III during the fifth time interval shows, this is a lapse in the increase, which was again followed by an exacerbation.

The further calculation also again agrees with the relationships found for the intermittent fever. For a healthy person of the given weight, the average

heat output during one-half hour would be about 42.5 calories. The fact that it is substantially smaller in a sick person can be explained, in part, by the wear created by the illness which lasts a long time. In part, this also is based on the fact that the entire observation time occurred during the increasing temperature phase (chill phase). In this case, the heat output was reduced the most at the time of most rapid increase in body temperature. /205

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